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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,677	10/17/2003	John Guy	5853-324	9515

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,677	GUY, JOHN	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *19-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner prosecuting this case has changed. All inquiries directed to the application should be directed to examiner W. - C. Winston Shen.

This application 10/687,677 filed on October 17, 2003 claims the benefit of 60/419,435 filed on 10/18/2002.

Election/Restriction

1. Applicant's election without traverse of Group I, claims 1-18, drawn to a non-naturally occurring nucleic acids encoding a functional ND4 mitochondrial protein, and isolated host cells (*in vitro*) comprising the same, in the reply filed on Oct. 5, 2006 is acknowledged.

Claims 19-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Status of claims: Claims 1-18 are currently under examination.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claim 7, which is a dependent claim of claim 1, reads on a non-naturally occurring nucleic acid *comprising* a nucleotide sequence of SEQ ID NO: 1 that (a) encodes a functional

ND4 mitochondrial protein and (b) that differs from a naturally occurring nucleic acid that encodes a ND4 mitochondrial protein by at least one codon substitution.

The specification has not taught SEQ ID NO: 1 of the claimed sequences that encode a functional ND4 mitochondrial protein. SEQ ID NO: 1 is a variant of SEQ ID No: 2 generated by replacing mitochondria codon with a nuclear codon. The skilled artisan would not be able to predict the structure of a variant that is biologically active because the specification has not provided any information as to the structural elements required for a ND4 mitochondrial protein to be biologically active. The specification does not provide any information on what amino acid residues encoded by the nucleic acid sequences are necessary and sufficient for biological activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant polypeptide encoded by SEQ ID No: 1 that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of a variant known that have structural homology with SEQ ID NO: 1, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7,

1976) discloses that even for peptide hormones, which are much smaller than the instant ND4 mitochondrial protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a biologically active ND4 mitochondrial protein with an amino acid sequence differing from amino acid sequences encoded by SEQ ID NO: 1 since the amino acid sequence of such polypeptides could not be predicted. Further, and more importantly even if such structure information were available, the skilled artisan would not be able to test any of the sequence variants because the specification has not provided an assay for determining biological activity of the claimed functional ND4 mitochondrial protein. The substrates and/or interacting proteins, which the alleged ND4 mitochondrial protein acts on, have not been disclosed. Thus, the skilled artisan would not know how to test any of the claimed variants for biological activity as required by the claims.

It would have required undue experimentation to predict the structures of variants to the claimed sequences that would be biologically active in the absence of a functional assay, without a reasonable expectation of success. As a related issue, it is worth noting that the nucleic acid sequences comprising a promoter with various regulatory elements that control the expression level of SEQ ID No: 1, and the nucleic acid sequence encoding variants of mitochondrial targeting signal will also affect the asserted biological function the ND4 mitochondrial protein.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 1 and 7.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 reads on a *non-naturally occurring* nucleic acid comprising a nucleotide sequence that (a) encodes a functional ND4 mitochondrial protein and (b) that differs from a naturally occurring nucleic acid that encodes a ND4 mitochondrial protein by at least one codon substitution. It is not clear what the nucleotide sequences encoding a functional ND4 mitochondrial protein are encompassed by the term "*non-naturally occurring*" because any base substitution at any position of the ND4 coding sequences could occur naturally by mutations either spontaneously or induced under certain environmental conditions in nature. Claims 2-18 depend from claim 1.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 8-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Guy (Guy, Gene therapy for nuclear complementation of the G11778A LHON mitochondrial DNA mutation, Neurology, (April 24, 2001) Vol. 56, No. 8 Supplement 3, pp. A14. print. Meeting Info.: 53rd Annual Meeting of the American Academy of Neurology. Philadelphia, PA, USA. May 05-11, 2001. American Academy of Neurology. CODEN: NEURAI. ISSN: 0028-3878). The teachings of Guy et al are recited in the next page.

With regard to the enhancer element (claim 13 of instant applicant), the recombinant Adeno-associated virus (AAV) vector taught by Guy reads on the CMV enhancer element because the CMV enhancer element is common composition of an AAV vector. This is evident and supported by Guy et al., Rescue of a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy. *Ann Neurol.* 52(5): 534-42, 2002, published online October 11, 2002.

OBJECTIVE: To recode a full length mitochondrial sequence (ND4) in the universal genetic code and deliver the recoded ND4 gene to cybrid cells containing the G11778A point mutation in mitochondrial DNA of Leber Hereditary Optic Neuropathy (LHON). Successful import of the wild-type ND4 subunit may reduce the degree of heteroplasmy of mutant to wild-type protein within the mitochondria, thus favoring a more normal functioning of the OXPHOS system and perhaps reducing the risk of visual loss in patients harboring this mtDNA mutation.

BACKGROUND: Unlike, mtDNA-encoded proteins, nuclear-encoded proteins that are synthesized within the cytoplasm are more hydrophilic, thus amenable to import into mitochondria by a cleavable mitochondrial targeting presequence. While targeting of less hydrophobic proteins back into mitochondria is not hard to achieve, mitochondrial encoded proteins are extremely hydrophobic and are difficult to import.

DESIGN/METHODS: The feasibility of complementing a mutation in the mitochondrial subunit ND4 (G11778A) was tested by construction of a nuclear encoded version of wild-type ND4. Codons read in a non-canonical fashion by the mitochondrial genetic system, such as the UGA codon that directs the insertion of tryptophan in mitochondria, but is a stop codon in the cytoplasm were converted to the universal genetic code. The coding sequence for a mitochondrial targeting peptide was appended to the reading frame and nuclear promoter and polyadenylation sequences were provided. Cybrid cells derived from patients with LHON were transfected by calcium phosphate precipitation with the fusion gene containing the mitochondrial targeting sequence linked to nuclear encoded ND4 and a short sequence encoding the Flag protein. Mitochondrial import of the fusion ND4-Flag protein was detected by immunofluorescence with a murine anti-flag antibody 2 days after transfection. Mitochondria were identified by a rabbit polyclonal antibody against SOD2 or by Mitotracker. To determine whether cybrids can be used as a model system to detect an improvement in OXPHOS by the gene transfer, the rate of ATP synthesis using complex 1 substrates (malate and pyruvate) was measured in the cybrids and compared to a control cell line with normal mtDNA.

RESULTS: Anti-flag immunofluoresence revealed successful import of the ND4flag fusion protein into approximately 5–10% of the transfected G11178A cybrid cells. The rate of ATP synthesis in the cybrids was reduced 63% (12.6 mM ATP/minute/10^7 cells) relative to the control cell line (29.5 mM ATP/minute/10^7 cells).

CONCLUSIONS: Successful import of the recoded ND4 together with the reduction of OXPHOS in the cybrids sets the stage for future experiments to clone the ND4-flag fusion gene into recombinant adenoassociated virus to increase the population of tranduced cybrid cells, then determination whether the recoded ND4 improves OXPHOS in the transduced cells.

5. Claims 1-6, and 8-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Guy et al. (Guy et al., Rescue of a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy. *Ann Neurol.* 52(5): 534-42, 2002, published online *October 11, 2002*).

Guy et al. teach that a G to A transition at nucleotide 11778 in the ND4 subunit gene of complex I was the first point mutation in the mitochondrial genome linked to a human disease. It causes Leber Hereditary Optic Neuropathy, a disorder with oxidative phosphorylation deficiency. To overcome this defect, Gut et al. made a synthetic ND4 subunit compatible with the "universal" genetic code and imported it into mitochondria by adding a mitochondrial targeting sequence. For detection, Guy et al. added a FLAG tag. This gene was inserted in an adeno-associated viral vector. The ND4FLAG protein was imported into the mitochondria of cybrids harboring the G11778A mutation, where it increased their survival rate threefold, under restrictive conditions that forced the cells to rely predominantly on oxidative phosphorylation to produce ATP. Since assays of complex I activity were normal in G11778A cybrids Guy et al. focused on changes in ATP synthesis using complex I substrates. The G11778A cybrids showed a 60% reduction in the rate of ATP synthesis. Relative to mock-transfected G11778A cybrids, complemented G11778A cybrids showed a threefold increase in ATP synthesis, to a level indistinguishable from that in cybrids containing normal mitochondrial DNA. Guy et al. state that the restoration of respiration by allotopic expression opens the door for gene therapy of Leber Hereditary Optic Neuropathy (See abstract, Guy et al.).

With regard to a cell being human nerve cell located in the optic nerve of a human subject (claims 15-18 of instant application), Guy et al teach that the successful restoration of

complex I-dependent respiration to a cell line still harboring the LHON G11778A mutation by allotopic expression of a normal ND4 subunit gene may be a promising step in a gene-based treatment for this blinding disorder. However, before this form of therapy can be applied to patients, several important issues need to be addressed, not the least of which is the precise pathophysiology causing LHON. Studies showing neuronal cell lines are more severely affected by the G11778A mtDNA mutation imply a relative vulnerability of neurons to this mutation, but why then is only the *optic nerve* destroyed in patients with the LHON mutation? Clearly, optic nerve degeneration is a feature of several different human diseases that include Leigh's syndrome, infantile bilateral striatal necrosis, Friedreich's ataxia, and dominant optic atrophy (OPA1), as well as LHON. Although each of these diseases affecting the optic nerve has in common mutated mitochondrial proteins, the selective vulnerability of the optic nerve in LHON remains somewhat a mystery. This key issue remains elusive in large part because of the absence of an LHON animal model to investigate the pathogenic effects of the G11778A mtDNA mutation in vivo in tissues rather than isolated *in vitro* in cultured cells. The lack of an LHON animal model is truly unfortunate; without one we are unable to test whether allotopic expression with a normal ND4 can rescue the oxidative phosphorylation deficiency of LHON and thus reverse or prevent blindness in vivo (See Discussion, page 539, Guy et al.).

6. Claims 1-2, 8, 10-12, 15-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Guy et al. (Guy et al., Gene therapy with the ND4 subunit gene recoded in the universal genetic code reverses a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy (LHON), Neurology, (April 9, 2002) Vol. 58, No. 7 Supplement 3, pp. A508. print. Meeting Info.: 54th

Annual Meeting of the American Academy of Neurology. Denver, Colorado, USA. April 13-20, 2002. CODEN: NEURAI. ISSN: 0028-3878). The teachings of Guy et al. are recited below.

OBJECTIVE: To rescue a deficiency in oxidative phosphorylation (OXPHOS) to a cybrid cell line harboring the G11778A LHON mutation in mitochondrial DNA.

BACKGROUND: While the pathophysiologic events precipitating visual failure and optic nerve injury in LHON are unknown, mitochondrial OXPHOS deficiency due to mutations in complex I subunit genes is believed to play a pivotal role.

DESIGN/METHODS: Cybrid cell lines created from patient's tissue with the LHON G11778A mitochondrial DNA (mtDNA) mutation in a normal nuclear background showed a 60% reduction in the rate of ATP synthesis. To overcome this deficiency, we re-coded the entire ND4 subunit of mtDNA using the universal genetic code (rND4), imported the translated protein into the mitochondria with a mitochondrial targeting sequence (allotopic expression) derived from the P1 isoform of subunit c of ATP synthase (ATPc). For detection of import a FLAG epitope tag was added at the C-terminus. The P1rND4F fusion gene was inserted in an adeno-associated viral (AAV) vector and LHON cybrid cells were transfected. Cells were grown in glucose-rich media, then placed in glucose-free medium containing galactose as the main carbon source for glycolysis. This medium forces the cells to rely predominantly on oxidative phosphorylation to produce ATP. Cells harboring complex I mutations have a severe growth defect in galactose medium.

RESULTS: FLAG immunochemistry revealed a typical punctate mitochondrial pattern that co-localized with the mitochondrion-specific dye MitoTracker Red, suggesting that P1rND4F was localized in mitochondria. Western blot analysis showed the imported P1rND4F fusion protein of a size consistent with that of the mature imported polypeptide. Cell survival after 3 days in the glucose deficient galactose media was 3-fold greater for the allotopically transfected P1rND4F cybrids than mock-transfected cybrids ($p<0.005$). Assays of complex I activity in whole cells by the reduction of cytochrome c with NADH revealed no significant reduction in G11778A cybrids compared to wild-type cybrids. Therefore, we focused on changes in ATP synthesis using the complex I substrates malate and pyruvate. Relative to control wild-type cell line, G11778A mutant cybrid cells showed a 60% reduction in the rate of ATP synthesis. Allotopic expression of ND4 reversed this deficiency in ATP synthesis. Relative to mock-transfected G11778A cybrids, G11778A cybrids complemented with P1rND4F showed a 3-fold increase in the rate of ATP synthesis ($p=0.02$). In fact, this degree of recovery lead to rates of ATP synthesis that were virtually indistinguishable from the corresponding wild-type cell line.

CONCLUSIONS: Restoration of ATP synthesis to a cell line harboring the LHON G11778A mutation by allotopic expression of a normal ND4 may be the initial step in a gene-based treatment for this blinding disorder.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-6, 8-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Manfredi et al. (Manfredi et al., U.S. Patent Application Publication No: 2004/0072774, Publication date, April15, 2004, which claims benefits of provisional application No. 60/358,935, filed on Feb. 23, 2002).

Manfredi et al. teach methods for introducing functional peptides into organelles. Additionally, the present invention provides a method for correcting a phenotypic deficiency in a mammal that results from a mutation in the mammal's mitochondrial DNA (mtDNA). The invention by Manfredi et al. further provides a method for treating a mitochondrial disorder in a subject in need of treatment therefor. Also provided is an expression vector that is useful for introducing a functional peptide encoded by an mtDNA sequence into a mitochondrion. The invention by Manfredi et al. also provides eukaryotic cells transformed by expression vectors that are useful for introducing functional peptides into organelles. Finally, the invention by Manfredi et al. provides a pharmaceutical composition comprising a non-nuclear nucleic acid sequence encoding a peptide for introduction into an organelle, a nucleic acid sequence encoding an organelle-targeting signal, and a pharmaceutically acceptable carrier (See abstract, Manfredi et al.).

With regard to a non-naturally occurring nucleic acid (claim 1 of instant application), Manfredi et al. teach an expression vector that is useful for introducing a functional peptide encoded by a mitochondrial DNA (mtDNA) sequence into a mitochondrion, comprising: (a) a nucleic acid sequence encoding ATPase 6 subunit of F_0F_1-ATP synthase or *ND4* subunit of complex I, wherein the nucleic acid sequence is compatible with the *universal genetic code*; and (b) a nucleic acid sequence encoding a mitochondrial-targeting signal, wherein the mitochondrial-targeting signal is selected from the group consisting of the N-terminal region of human cytochrome c oxidase subunit VIII, the N-terminal region of the P1 isoform of subunit c of human ATP synthase, and the N-terminal region of the aldehyde dehydrogenase targeting sequence (See claim 75, Manfredi et al.).

With regard to the codon substitution being replaced of a mitochondrial codon with a nuclear codon in construction of a nuclear version of functional ND4 mitochondrial protein (claims 2-6 of instant application), Manfredi et al. teach (i) 11 "non-universal" codons in MTATP6 (Met=ATA or ATG; Trp=TGA) (See Fig. 1, Manfredi et al.), (ii) the genetic system of mitochondria differs from other known genetic systems because it deviates from the standard, or "universal", genetic code in several ways. In particular, the UGA codon, which generally means "stop", codes for tryptophan in mammalian mitochondria; the AUA codon, which generally codes for isoleucine, codes for methionine in mammalian mitochondria; and the AGA codon, which generally codes for arginine, means "stop" in mammalian mitochondria. Accordingly, where a mitochondrial nucleic acid sequence is used in the method of the present invention, it may be necessary to first mutagenize the nucleic acid sequence to render it compatible with the universal genetic code. In such instances, a mutagenized mtDNA-specified

polypeptide is appended to a mitochondrial-targeting signal, expressed from the nucleus, and transported back to the mitochondria under the guidance of the signal peptide (See paragraph [0049], Manfredi et al.), (iii) a nucleic acid sequence encoding ATPase 6 subunit of F_0F_1-ATP synthase or *ND4* subunit of complex I, wherein the nucleic acid sequence is compatible with the *universal genetic code* (See for instance, paragraph [0020] and claim 75, Manfredi et al.), (iv) construction of recorded ND4F and Adeno-Associated virus vectors (See example 7, Manfredi et al.), and (v) strategy for allotropic expression of ND4 and allotropic ND4 improves cybrid cell survival (See example 10, Manfredi et al.).

With regard to the components of an expression vector (claims 8-14 of instant application), Manfredi et al. teach preparation of constructs (See example 1, Manfredi et al.).

With regard to a cell being a human cell located in the optic nerve of a human (claims 15-18 of instant application), Manfredi et al. teach stable and efficient expression of the fusion gene in cells, (See paragraph [0123], Manfredi et al.).

Conclusion

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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